

<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
USPT	116 and ("t.sub.m" or melting temperature or binding constant)	8	<u>L17</u>
USPT	114 and (nucleotide same "2'-o")	34	<u>L16</u>
USPT	114 and (ribosyl same "2'-o")	0	<u>L15</u>
USPT	modifi\$9 same "2'-o"	118	<u>L14</u>
USPT	increased binding same "2'-o"	0	<u>L13</u>
USPT	increased stability same "2'-o"	0	<u>L12</u>
USPT	18 and 110	6	<u>L11</u>
USPT	17 and (hybridization same assay)	28	<u>L10</u>
USPT	17 and (hybridization and assay)	37	<u>L9</u>
USPT	17 and array	14	<u>L8</u>
USPT	16 and (oligonucleotide or dna or rna)	55	<u>L7</u>
USPT	(melting same temperature) and "2'-O"	154	<u>L6</u>
USPT	14 and (dna or rna or nucleotide or nucleoside)	0	<u>L5</u>
USPT	("t.sub.m") same ("2'-O")	3	<u>L4</u>
USPT	11 and (melting same temperature)	1	<u>L3</u>
USPT	11 and "t.sub.m"	0	<u>L2</u>
USPT	05986083 or 05861242	2	<u>L1</u>

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Search Results - Record(s) 1 through 8 of 8 returned.☐ 1. Document ID: US 6084102 A

L17: Entry 1 of 8

File: USPT

Jul 4, 2000

US-PAT-NO: 6084102

DOCUMENT-IDENTIFIER: US 6084102 A

TITLE: Covalently linked oligonucleotide minor groove binder conjugates

DATE-ISSUED: July 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kutyavin; Igor V.	Bothell	WA	N/A	N/A
Lukhtanov; Eugeny A.	Bothell	WA	N/A	N/A
Gamper; Howard B.	Woodinville	WA	N/A	N/A
Meyer, Jr.; Rich B.	Woodinville	WA	N/A	N/A

US-CL-CURRENT: 548/100

ABSTRACT:

Minor groove binding molecules are covalently bound to oligonucleotides which in their base sequence are complementary to a target sequence of single stranded or double stranded DNA, RNA or hybrids thereof. The covalently bound oligonucleotide minor groove binder conjugates strongly bind to the target sequence of the complementary strand.

17 Claims, 0 Drawing figures Exemplary Claim Number: 1

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWNC	Draw Desc	Image
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☐ 2. Document ID: US 6005087 A

L17: Entry 2 of 8

File: USPT

Dec 21, 1999

US-PAT-NO: 6005087

DOCUMENT-IDENTIFIER: US 6005087 A

TITLE: 2'-modified oligonucleotides

DATE-ISSUED: December 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cook; Phillip Dan	Carlsbad	CA	N/A	N/A
Kawasaki; Andrew Mamoru	Oceanside	CA	N/A	N/A

US-CL-CURRENT: 536/23.1; 536/23.5, 536/24.31, 536/24.32, 536/24.5

ABSTRACT:

Compositions and methods are provided for the treatment and diagnosis of diseases amenable to modulation of the production of selected proteins. In accordance with preferred embodiments, oligonucleotides and oligonucleotide analogs are provided which are specifically hybridizable with a selected sequence of RNA or DNA wherein at least one of the 2'-deoxyfuranosyl moieties of the nucleoside unit is modified. Treatment of diseases caused by various viruses and other causative agents is provided.

3 Claims, 9 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 9

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMC	Draw Desc	Image
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☐ 3. Document ID: US 5872232 A

L17: Entry 3 of 8

File: USPT

Feb 16, 1999

US-PAT-NO: 5872232

DOCUMENT-IDENTIFIER: US 5872232 A

TITLE: 2'-O-modified oligonucleotides

DATE-ISSUED: February 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cook; Phillip Dan	San Marcos	CA	N/A	N/A
Kawasaki; Andrew Mamoru	Oceanside	CA	N/A	N/A

US-CL-CURRENT: 536/23.1; 435/375, 435/6, 435/91.1, 536/24.3, 536/24.5

ABSTRACT:

Compositions and methods are provided for the treatment and diagnosis of diseases amenable to modulation of the production of selected proteins. In accordance with preferred embodiments, oligonucleotides and oligonucleotide analogs are provided which are specifically hybridizable with a selected sequence of RNA or DNA wherein at least one of the 2'-deoxyfuranosyl moieties of the nucleoside unit is modified. Treatment of diseases caused by various viruses and other causative agents is provided.

15 Claims, 9 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 9

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 4. Document ID: US 5872242 A

L17: Entry 4 of 8

File: USPT

Feb 16, 1999

US-PAT-NO: 5872242

DOCUMENT-IDENTIFIER: US 5872242 A

TITLE: Antisense oligonucleotide inhibition of ras

DATE-ISSUED: February 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Monia; Brett P.	La Costa	CA	N/A	N/A
Cowsert; Lex M.	Carlsbad	CA	N/A	N/A
Manoharan; Muthiah	Carlsbad	CA	N/A	N/A

US-CL-CURRENT: 536/24.5; 435/5, 435/6, 435/91.2, 536/23.1, 536/24.3, 536/24.31, 536/24.33

ABSTRACT:

Compositions and methods are provided for the modulation of ras expression. Oligonucleotides are provided which are targeted to nucleic acids encoding human ras. Oligonucleotides specifically hybridizable with mRNA encoding human H-ras, Ki-ras and N-ras are provided. Such oligonucleotides can be used for therapeutics and diagnostics as well as for research purposes. Methods are also disclosed for modulating ras gene expression in cells and tissues using the oligonucleotides provided, and for specific modulation of expression of activated ras. Methods for diagnosis, detection and treatment of conditions associated with ras are also disclosed.

8 Claims, 17 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 12

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 5. Document ID: US 5859221 A

L17: Entry 5 of 8

File: USPT

Jan 12, 1999

US-PAT-NO: 5859221

DOCUMENT-IDENTIFIER: US 5859221 A

TITLE: 2'-modified oligonucleotides

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cook; Phillip Dan	San Marcos	CA	N/A	N/A
Kawasaki; Andrew Mamoru	Oceanside	CA	N/A	N/A

US-CL-CURRENT: 536/23.1; 435/6, 435/91.1, 435/91.3, 536/24.5, 536/25.3

ABSTRACT:

Compositions and methods are provided for the treatment and diagnosis of diseases amenable to modulation of the production of selected proteins. In accordance with preferred embodiments, oligonucleotides and oligonucleotide analogs are provided which are specifically hybridizable with a selected sequence of RNA or DNA wherein at least one of the 2'-deoxyfuranosyl moieties of the nucleoside unit is modified. Treatment of diseases caused by various viruses and other causative agents is provided.

6 Claims, 9 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 9

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 6. Document ID: US 5801155 A

L17: Entry 6 of 8

File: USPT

Sep 1, 1998

US-PAT-NO: 5801155

DOCUMENT-IDENTIFIER: US 5801155 A

TITLE: Covalently linked oligonucleotide minor groove binder conjugates

DATE-ISSUED: September 1, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kutyavin; Igor V.	Bothell	WA	N/A	N/A
Lukhtanov; Eugeny A.	Bothell	WA	N/A	N/A
Gamper; Howard B.	Woodinville	WA	N/A	N/A
Meyer, Jr.; Rich B.	Woodinville	WA	N/A	N/A

US-CL-CURRENT: 514/44; 514/419, 534/727, 536/25.3, 536/25.32, 546/112, 546/114,
546/115, 546/118, 546/268.7, 546/269.1, 546/269.7, 546/271.4, 546/272.7,
546/275.4, 546/276.4, 548/311.1, 548/312.4

ABSTRACT:

Minor groove binding molecules are covalently bound to oligonucleotides which in their base sequence are complementary to a target sequence of single stranded or double stranded DNA, RNA or hybrids thereof. The covalently bound oligonucleotide minor groove binder conjugates strongly bind to the target sequence of the complementary strand.

28 Claims, 1 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMC	Draw Desc	Image
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☐ 7. Document ID: US 5719271 A

L17: Entry 7 of 8

File: USPT

Feb 17, 1998

US-PAT-NO: 5719271

DOCUMENT-IDENTIFIER: US 5719271 A

TITLE: Covalently cross-linked oligonucleotides

DATE-ISSUED: February 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cook; Phillip Dan	Carlsbad	CA	N/A	N/A
Manoharan; Muthiah	Carlsbad	CA	N/A	N/A
Bruice; Thomas	Carlsbad	CA	N/A	N/A

US-CL-CURRENT: 536/23.1; 536/24.3, 536/24.5

ABSTRACT:

Covalent cross-linkages for two oligonucleotide strands or for first and second regions of a single oligonucleotide strand connect sugar moieties of nucleotides on the respective strands or the regions of the single strand. The cross-linkages are connected to at least one strand or region via a space-spanning group. The cross-linkage also can be connected to the other strand or other region via a space-spanning group or via an abasic site located on the other strand or other region.

22 Claims, 0 Drawing figures Exemplary Claim Number: 1

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KIMC	Draw Desc	Image
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☐ 8. Document ID: US 5543507 A

L17: Entry 8 of 8

File: USPT

Aug 6, 1996

US-PAT-NO: 5543507

DOCUMENT-IDENTIFIER: US 5543507 A

TITLE: Covalently cross-linked oligonucleotides

DATE-ISSUED: August 6, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cook; Phillip D.	Carlsbad	CA	N/A	N/A
Manoharan; Muthiah	Carlsbad	CA	N/A	N/A
Bruice; Thomas	Carlsbad	CA	N/A	N/A

US-CL-CURRENT: 536/23.1; 435/91.1, 435/91.21, 435/91.4, 435/91.5, 536/24.1, 536/24.2, 536/24.3, 536/24.31, 536/24.32, 536/24.33, 536/25.2, 536/25.3

ABSTRACT:

Covalent cross-linkages for two oligonucleotide strands or for first and second regions of a single oligonucleotide strand connect sugar moieties of nucleotides on the respective strands or the regions of the single strand. The cross-linkages are connected to at least one strand or region via a space-spanning group. The cross-linkage also can be connected to the other strand or other region via a space-spanning group or via an abasic site located on the other strand or other region.

77 Claims, 0 Drawing figures Exemplary Claim Number: 1

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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Terms

116 and ("t.sub.m" or melting temperature or binding constant)

Documents

8

☐ Documents, starting with Document: Display Format:

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L17: Entry 2 of 8

See Claim 1

File: USPT

Dec 21, 1999

DOCUMENT-IDENTIFIER: US 6005087 A
TITLE: 2'-modified oligonucleotides*May have been art against
originally presented claims
1-15*

BSPR:

The relative ability of an oligonucleotide to bind to complementary nucleic acids is compared by determining the melting temperature of a particular hybridization complex. The melting temperature ($T_{sub.m}$), a characteristic physical property of double helices, is the temperature (in .degree. C.) at which 50% helical versus coil (unhybridized) forms are present. $T_{sub.m}$ is measured by using UV spectroscopy to determine the formation and breakdown (melting) of hybridization. Base stacking, which occurs during hybridization, is accompanied by a reduction in UV absorption (hypochromicity). Consequently, a reduction in UV absorption indicates a higher $T_{sub.m}$. The higher the $T_{sub.m}$ the greater the strength of the binding of the nucleic acid strands.

BSPR:

Furthermore, evidence has been presented which indicates that 2'-substituted-2'-deoxyadenosine polynucleotides resemble double-stranded RNA rather than DNA. Ikehara et al. [Nucleic Acids Res., 5, 3315 (1978)] have shown that a 2'-fluoro substituent in poly A, poly I, or poly C duplexed to its complement is significantly more stable than the ribonucleotide or deoxyribonucleotide poly duplex as determined by standard melting assays. Ikehara et al. [Nucleic Acids Res., 4, 4249 (1978)] have shown that a 2'-chloro or bromo substituent in poly(2'-deoxyadenylic acid) provides nuclease resistance. Eckstein et al. [Biochemistry, 11, 4336 (1972)] have reported that poly(2'-chloro-2'-deoxyuridylic acid) and poly(2'-chloro-2'-deoxycytidylic acid) are resistant to various nucleases. Inoue et al. [Nucleic Acids Research, 15, 6131 (1987)] have described the synthesis of mixed oligonucleotide sequences containing 2'-OMe substituents on every nucleotide. The mixed 2'-OMe-substituted oligonucleotide hybridized to its RNA complement as strongly as the RNA-RNA duplex which is significantly stronger than the same sequence RNA-DNA heteroduplex ($T_{sub.m}$ s, 49.0 and 50.1 versus 33.0 degrees for nonamers). Shibahara et al. [Nucleic Acids Research, 17, 239 (1987)] have reported the synthesis of mixed oligonucleotides containing 2'-OMe substituents on every nucleotide. The mixed 2'-OMe-substituted oligonucleotides were designed to inhibit HIV replication.

DEPR:

This invention provides oligonucleotides possessing superior hybridization properties. Structure-activity relationship studies have revealed that an increase in binding ($T_{sub.m}$) of certain 2'-sugar modified oligonucleotides to an RNA target (complement) correlates with an increased "A" type conformation of the heteroduplex. Furthermore, absolute fidelity of the modified oligonucleotides is maintained. Increased binding of 2'-sugar modified sequence-specific oligonucleotides of the invention provides superior potency and specificity compared to phosphorus-modified oligonucleotides such as methyl phosphonates, phosphate triesters and phosphoramidates as known in the literature.

DEPR:

The 2'-iodo substituted nucleosides possess the lowest C3'-endo population (7%) of the halogen series. Thus, based solely on steric effects, one would predict that a 2'-iodo (or other similar group) would contribute stacking

destabilization properties, and thus reduced binding ($T_{sub.m}$) of the oligonucleotides. However, the lower electronegativity and high hydrophobicity of the iodine atom (or another similar group) complicates the ability to predict stacking stabilities and binding strengths.

DEPR:

Melting temperatures (complementary binding) are increased with the 2'-substituted adenosine diphosphates. It is not clear whether the 3'-endo preference of the conformation or the presence of the substituent is responsible for the increased binding. However, greater overlap of adjacent bases (stacking) can be achieved with the 3'-endo conformation.

DEPR:

Illustrative 2'-O-alkyl (2'-alkoxy) modified oligonucleotides are prepared from appropriate precursor nucleotides that in turn are prepared starting from a commercial nucleoside. The nucleoside, either unblocked or appropriately blocked as necessary to protect exocyclic functional groups on their heterobases, are alkylated at the 2'-O position. This 2'-O-alkylated nucleosides is converted to a 5'-O-dimethoxytrityl protected nucleosides and 3'-O-phosphitylated to give a phosphoramidite. The phosphoramidites are incorporated in oligonucleotides using standard machine cycle solid phase phosphoramidite oligonucleotide chemistry. For illustrative purposes the synthesis of 2'-O-nonyladenosine, 2'-O-propyluridine, 2'-O-methylcytidine, 2'-O-octadecylguanosine, 2'-O-[(N-phthalimido)prop-3-yl]-N^{sup.6}-benzoyladenosine and 2'-O-[(imidazol-1-yl)but-4-yl]adenosine are given. Other 2'-O-alkylated nucleosides are prepared in a like manner using an appropriate starting alkyl halide in place of the illustrated alkyl halides. For certain 2'-O-aminoalkyl compounds of the invention, protected amines, e.g. phthalimido, were used during alkylation, subsequent tritylation and phosphitylation. After incorporation into the oligonucleotide of interest, the 2'-O-protected aminoalkyl moiety are deblocked to yield the free amino compound, i.e. 2'-O-(CH_{sub.2})_{sub.n} --NH_{sub.2}.

DEPR:

As is evident from Table 1, the duplexes formed between RNA and oligonucleotides containing 2'-deoxy-2'-fluoro substituted nucleotides exhibited increased binding stability as measured by the hybridization thermodynamic stability. $\Delta T_{sub.m}$ s of greater than 20.degree. C. were measured. By modifying the backbone to a phosphorothioate backbone, even greater $\Delta T_{sub.m}$ s were observed. In this instance, $\Delta T_{sub.m}$ s greater than 31.degree. C. were measured. These fluoro-substituted oligonucleotides exhibited a consistent and additive increase in the thermodynamic stability of the duplexes formed with RNA. While we do not wish to be bound by theory, it is presently believed that the presence of a 2'-fluoro substituent results in the sugar moiety of the 2'-fluoro-substituted nucleotide assuming substantially a 3'-endo conformation and this results in the oligonucleotide-RNA complex assuming an A-type helical conformation.

DEPR:

A 15 mer RNA target of the sequence 5'GCGTTTTTTTTTGGCG 3' (SEQ ID NO:32) was prepared in the normal manner on the DNA sequencer using RNA protocols. A series of complementary phosphorothioate oligonucleotides having 2'-O-substituted nucleotides in regions that flank a 2'-deoxy region were prepared utilizing 2'-O-substituted nucleotide precursors prepared as per known literature preparations, i.e. 2'-O-methyl, or as per the procedure of International Publication Number WO 92/03568, published Mar. 5, 1992. The 2'-O-substituted nucleotides were added as their 5'-O-dimethoxytrityl-3'-phosphoramidites in the normal manner on the DNA synthesizer. The complementary oligonucleotides have the sequence of 5'CGCAAAAAAAAAAACGC 3' (SEQ ID NO:33). The 2'-O-substituent was located in CGC and CG regions of these oligonucleotides. The following 2'-O-substituents were used: 2'-fluoro; 2'-O-methyl; 2'-O-propyl; 2'-O-allyl; 2'-O-aminopropoxy; 2'-O-(methoxyethoxyethyl), 2'-O-imidazolebutoxy and 2'-O-imidazolepropoxy.

DEPR:

Absorbance vs. temperature curves were measured at 260 nm using a Gilford 260 spectrophotometer interfaced to an IBM PC computer and a Gilford Response II spectrophotometer. The buffer contained 100 mM Na^{sup.}+, 10 mM phosphate and 0.1 mM EDTA, pH 7. Oligonucleotide concentration was 4 .mu.M each strand determined from the absorbance at 85.degree. C. and extinction coefficients calculated according to Puglisi and Tinoco [Methods in Enzymol., 180, 304 (1989)]. T.sub.m values, free energies of duplex formation and association constants were obtained from fits of data to a two state model with linear sloping baselines. [Petersheim and Turner, Biochemistry, 22, 256 (1983)]. Reported parameters are averages of at least three experiments. For some oligonucleotides, free energies of duplex formation were also obtained from plots of T.sub.m.sup.-1 vs log.sub.10 (concentration). Borer et al., J. Mol. Biol., 86, 843 (1974).

DEPL:

Other sugar modifications: The effects of other 2' sugar modifications besides 2'-O-methyl on antisense activity in chimeric oligonucleotides have been examined. These modifications are listed in Table 4, along with the T.sub.m values obtained when 17 mer oligonucleotides having 2'-modified nucleotides flanking a 7-base deoxy gap were hybridized with a 25 mer oligoribonucleotide complement as described in Example 25. A relationship was observed for these oligonucleotides between alkyl length at the 2' position and T.sub.m. As alkyl length increased, T.sub.m decreased. The 2'-fluoro chimeric oligonucleotide displayed the highest T.sub.m of the series.

DETL:

TABLE 1

EFFECTS OF 2'-DEOXY-2'-FLUORO MODIFICATIONS ON DNA (ANTISENSE) RNA (SENSE) DUPLEX STABILITY G.degree.37 G.degree.37 T.sub.m (.degree.C.) / Antisense Sequence (kcal/mol) (kcal/mol) T.sub.m (.degree.C.) T.sub.m (.degree.C.) subst.

										CGA				
CTA	TGC	AAG	TAC	-10.11	+-	0.04	45.1	(SEQ ID NO:21)	CGA	CTA	TGC	AAG	TA	C
-13.61	+-	0.08	-3.50	+-	0.09	53.0	+ 7.9	+ 1.6	(SEQ ID NO:21)	CGA	CUA	UGC		
AAG	UAC	-16.18	+-	0.08	-6.07	+-	0.09	58.9	+ 13.8	+ 1.7	(SEQ ID NO:24)	CGA		
CUA	UGC	AAG	UAC	-19.85	+-	0.05	-9.74	+-	0.06	65.2	+ 20.1	+ 1.8	(SEQ ID NO:24)	ps(CGA CTA TGC AAG TAC) -7.58 +- 0.06 33.9 -11.2 (SEQ ID NO:21)
														ps(CGA CUA UGC AAG UAC) -15.90 +- 0.34 -8.32 +- 0.34 60.9 + 27.0 + 2.5 (SEQ ID NO:24) CTC GTA CCT TCC GGT CC -14.57 +- 0.13 61.6 (SEQ ID NO:22) CUC GUA CCU UCC GGU CC -27.81 +- 0.05 -13.24 +- 0.14 81.6 + 1.4 (SEQ ID NO:28)

DETL:

TABLE 2

EFFECTS OF SINGLE BASE MISMATCHES ON 2'-DEOXY-2'- FLUORO MODIFIED DNA-RNA DUPLEX STABILITY G.degree.37 G.degree.37 T.sub.m T.sub.m Y Base pair type (kcal/mol) (kcal/mol) (.degree.C.) (.degree.C.) X strand: deoxy(CTC GTA CCT TTC CGG TCC) (SEQ ID NO:29) Y strand: ribo(.sup.3 'GAG CAU GGY AAG GCC AGG.sup.5 ') (SEQ ID NO:30) A Watsan-Crick -14.57 +- 0.13 61.6 C T-C mismatch -12.78 +- 0.11 1.79 +- 0.17 54.4 -7.2 G T-G mismatch -16.39 +- 0.25 -1.82 +- 0.28 61.7 0.1 U T-U mismatch -13.48 +- 0.17 1.09 +- 0.22 55.9 -5.7 None Bulged T -14.86 +- 0.35 -0.284 +- 0.37 59.4 -2.2 X strand: deoxy(CUC GUA CCU UUC CGG UCC) (SEQ ID NO:31) Y strand: ribo(.sup.3 'GAG CAU GGY AAG GCC AGG.sup.5 ') (SEQ ID NO:30) A Watsan-Crick -27.80 +- 0.05 81.6 C U-C mismatch -21.98 +- 0.28 5.82 +- 0.28 73.8 -7.8 G U-G mismatch -21.69 +- 0.16 6.12 +- 0.17 77.8 -3.8 U U-U mismatch -18.68 +- 0.15 9.13 +- 0.16 73.6 -8.0 None Bulged U -22.87 +- 0.27 4.94 +- 0.27 75.5 -6.2

DETL:

TABLE 4

Correlation of T.sub.m with Antisense Activity 2'-modified 17-mer with 7-deoxy gap CCACACCGACGGCGCCC (SEQ ID NO: 1) 2' MODIFICATION IC.sub.50 (nM) Tm (.degree. C.)

O-Propyl	7	0	.	4	70	O-Methyl	7	4	.	7	20	Deoxy	6	4	.	2	150	O-Pentyl	6	8	.	5	150
												Fluoro	7	6	.	9	10						
